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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,149	06/30/2006	Christopher Robert Bebbington	073678-0026	9929

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EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/585,149	BEBBINGTON ET AL.	
	Examiner	Art Unit	
	CELINE X. QIAN	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48,54-78 and 80-117* is/are pending in the application.

4a) Of the above claim(s) *65-72,74,78,80-92,94-99,101,102 and 107-109* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48,55-64,75-77,93,100,103-106 and 110-117* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 48, 54-78, 80-117 are pending in the application. Claims 65-72, 74, 78, 80-92, 94-99, 101, 102, 107-109 are withdrawn from consideration. Claims 48, 55-64, 75-77, 93, 100, 103-106, 110-117 are currently under examination.

This Office Action is in response to the Amendment filed on 7/7/2010.

All rejections set forth in the previous office action which are not reiterated in this office action have been withdrawn.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 48, 55-64, 75-77, 93, 100, 103-106, 110-117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reff, Cockett and Rao et al., in view of Antoniou et al (WO 00/05393, see IDS).

Reff et al. teach preventing and delaying apoptosis by expressing one or more anti-apoptotic polypeptides such as E1B-19K and Aven in the cell (see page 5, [0013]), wherein the expression of said anti-apoptotic protein results in the increased production of a cell related product, such as an antibody to anti-CD20 antibodies etc (see page 5, [0014]). Reff et al. teach that such suitable host cells for large scale production of recombinant protein may be CHO cells, BHK cells or COS cells (page 11, [0050]).

However, Reff et al. do not teach expression vector encoding the polypeptide of interest is under the control of a promoter that responds to a transactivator, and the inclusion of IRES, UCOE, and use retroviral vector.

Cockett et al. teach vectors expressing adenovirus 5 E1A or mutant are introduced into CHO-K1 cells in order to transactivate the hCMV-MIE promoter. Cockett et al. teach that hCMV-MIE promoter is highly efficient in CHO cells (see page 319, 2nd col., 2nd paragraph, line 1). Cockett et al. demonstrate that E1A protein and its mutant can activate the activity of hCMV-MIE promoter in CHO cells, and increases the production of TIMP in cell culture (see Table 1, and page 321, 1st col., 2nd paragraph). Cockett et al. further teach that high level expression of E1A, however, is toxic to cells (see page 322, 1st col., 3rd paragraph).

Rao et al. teach expression of adenovirus E1A protein renders cell susceptible to apoptosis (see page 7743, 2nd col., 2nd and 3rd paragraph). Rao et al. further teach that expression

of E1B-19K and Bcl-2 protects cell from E1A induced apoptosis (page 7743, 2nd col., 4th paragraph, and 7745, Figure 5 and legend).

Antoniou et al. teach the isolation of a polynucleotide comprising a ubiquitous chromatin opening element from hnRNP promoter, which comprises an extended methylation free CpG island. Antoniou et al. teach that such UCOE maintains stable expression of exogenous gene in recombinant cells (see page 84, lines 1-28). Antoniou et al. also teach the inclusion of IRES in vector for expressing foreign gene (see page 13, line 25), and the vectors may be integration vectors such as retroviral vectors (see page 14, lines 6-15).

It would have been obvious to an ordinary skill in the art to transfect a vector encoding a transactivator such as E1A into the recombinant host cell for producing a polypeptide of interest such as a recombinant antibody based on the combined teaching of Reff et al., Cockett et al. and Rao et al. The ordinary skill in the art would realize the advantage of using such transactivator because Cockett et al. have demonstrated that said protein can transactivate the activity of hCMV-MIE, a promoter commonly used in CHO cells for producing recombinant protein. The ordinary skill in the art would recognize that use of such transactivator at high level may induce apoptosis of the host cell, which is not desirable for producing recombinant protein, and therefore, transfecting a apoptosis protecting protein to overcome such toxicity based on the teaching of Rao et al. Since Rao et al. already demonstrated the feasibility of inhibiting apoptosis by expressing E1B-19K and Bcl-2 in BHK cells, and Reff also demonstrate that expressing E1B-19K and Aven can protect cells from apoptosis in CHO cells, absent evidence from the contrary, the ordinary skill in the art would have reasonable expectation of success to develop a system comprising vectors that express E1A, Bcl-2 and/or E1B, and transfecting them

to recombinant protein producing host cells such as BHK or CHO to increase the production of recombinant protein. It would also have been obvious to an ordinary skill in the art to include cis element such as the hnRNP UCOE and IRES to the vector system discussed by Reff, Rao and Cockett for producing recombinant protein, as well as use retroviral vectors in such vector system. The ordinary artisan would have recognize that use of such elements would maintain stable expression of the foreign gene in a host cell (UCOE), and increase the expression of the second gene in the same vector (IRES) based on the teaching of Antoniou et al. Retroviral vectors are widely used for expressing foreign gene at the time of filing. Newly added claims 110-117 recite two fold increase and 5 fold increase in the production rate for the polypeptide of interest by combination of the transactivator and the apoptotic-protective protein. Since it is obvious to make such combination as demonstrated by Reff, Cockett and Rao, it is inherent that the production would be increased to the level as claimed. Combining prior art known elements to improve a known system based on their intended function would have been obvious to an ordinary skill in the art. Therefore, the claimed invention would have been *prima facie* obvious to the ordinary artisan at the time the invention was made.

Response to Arguments

In the response filed on 7/7/10, Applicants assert that the pending claims are not obvious because Reff publication teaches enhanced host performance when host cell life is extended beyond limiting factors that contribute to apoptosis through the use of apoptosis protective agent, wherein expressing a transactivator that would induce apoptosis would not be desirable. Applicants also assert that the teaching of Cockett indicate that expressing low levels of transactivator does not stop cell growth and the expression of a desired protein. Applicants

further assert that Rao and Antoniou both fail to teach expressing the transactivator at a toxic level. Applicants further cited Federal Circuit decision *Kinetic Concepts, Inc, v. Blue Sky Med. Grp, Inc.,* to address the combined teaching of Reff, Cockett, Rao and Antoniou do not teach the limitation of "expressing the transactivator at a level that could cause death of the host cell in the absence of the apoptosis protective protein, and wherein the apoptosis protective protein prevents cell death from the transactivator" just as they do not address "treating a wound with negative pressure" in this case. Applicants thus conclude that the claimed invention is not obvious in view of the combined teaching of Reff, Cockett, Rao and Antoniou.

This argument has been fully considered but deemed unpersuasive. First, Applicants are reminded that claims 48, 54, 55, 75-77 do not recite the limitation of "expressing the transactivator at a level that could cause death of the host cell in the absence of the apoptosis protective protein, and wherein the apoptosis protective protein prevents cell death from the transactivator," therefore, this argument does not apply to claims 48, 54, 55, 75-77. Second, the examiner would like to point out that the decision of *Kinetic Concepts, Inc, v. Blue Sky Med. Grp, Inc.* does not apply to the instant case because the factual basis are different between the decision and current application. The Federal decision reached the conclusion of non-obviousness based on the construction of the term "wound" which is defined by that specification being exclusively skin wound, not other types of injury taught by the prior art. In the instant case, the teaching of the specification does not render the combined teaching of prior art non-obvious because the specification does not provide a limiting definition for such level of expression or set forth a range for the expression level. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references

individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Reff has demonstrated that increased production of a polypeptide of interest as a result of expressing the anti-apoptotic protein, which indicate that even high level of expression of the transactivator which may normally be toxic to the cell can be protected from such toxicity with the co-expression of an anti-apoptotic protein. The teaching of Rao reinforces this notion. Therefore, the claimed invention is obvious in view of the teaching of the cited art for reason given above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56-64, 93, 100, 103-106 and 110-117 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. <u>This is a new matter rejection.</u>

Claims 56, 62, 93, 100 have been amended to recite a new limitation "wherein the transactivator is expressed at a level that could cause host cell death without an apoptosis protective protein...wherein the apoptosis protective protein prevents death of the host cell from the transactivator." This newly added limitation is not supported by the specification as originally filed. The specification does not describe expressing the transactivator at a level that

could cause death without an apoptosis protective protein, and does not describe such a toxic expression level or a range of such toxic level of said transctivator. Therefore, this newly added limitation constitutes new matter. Claims 57-64, 103-106 and 110-117 are rejected for depending on claims 56, 62, 93 and 100. Moreover, newly presented claims 110-117 recite the limitation of production rate of the antibody being enhanced at least two fold or five fold by the combination of the transactivator and the apoptosis protective protein. This newly added limitation is not supported by the specification as originally filed because the specification does not describe the combination of expressing the transactivator and the apoptosis protective protein would enhance the production rate of an antibody to at least two fold or five fold. Therefore, this newly added limitation constitutes new matter.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian /
Primary Examiner, Art Unit 1636